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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/181,311	10/28/1998	ARTHUR M. E. LEE	APV-382.01	9754

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EXAMINER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/181,311	Applicant(s) Lee et al
	Examiner Sharon L. Turner, Ph.D.	Art Unit 1647

-- The MAILING DATE of this communication appears on th cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 4-18-02

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 7-9 and 31-38 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 7-9 and 31-38 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-18-02 has been entered.

2. The amendment filed 12-27-01 has been entered into the record and has been fully considered.

3. Claims 1-6 and 10-30 have been canceled. Claims 7-9 and 31-38 are pending.

Rejections Maintained

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 7-9 and 31-38 stand rejected under 35 U.S.C. 101 as set forth in Paper No. 11 (8-16-00) and 15(5-9-01) because the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility.

Claims 7-9 and 31-38 also stand rejected under 35 U.S.C. 112, first paragraph as set forth in Paper No. 11 (8-16-00) and 15 (5-9-01). Specifically, since the claimed invention is not

supported by either a specific and substantial, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants note their previous arguments that genes identified as being up- or down regulated during differentiation or migration of smooth muscle cells are specifically useful as diagnostic markers of numerous diseases as specified at pp. 1-2 and p. 45, lines 9-23 as well as the Examiner's previous response. Applicants argue that the guidelines state that "an assay method for identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use", as in the definition of "substantial utility". Applicants conclude that since the claimed assay methods identify genes which themselves have a substantial utility, the assay methods define a real world context of use.

Applicant's arguments filed 12-27-01 have been fully considered but are not persuasive. Applicant's argument presupposes that the genes identified by the method will themselves have a substantial utility. Yet the specification and claims are not directed to any particular genes which are capable of being identified which themselves have been shown to possess substantial utility. The definition as set forth in the utility guidelines make it clear that, "utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities." The instant assay fails to correlate any particular gene product with any particular disease, but merely contemplates that such could be discovered by screening for players which are up- or down-regulated in a differentiating model system. While

e.g., an occlusive arteriosclerotic disease is contemplated by the specification as being a disease which would be likely to be associated with genes which were up- or down-regulated as claimed, no correlation between any such particular gene product ans occlusive arteriosclerotic disease in patients has been disclosed. The "substantial utility" definition in examples A-E make clear those utilities which cannot be considered as substantial including utilities wherein basic research is involved, methods of treating unspecified diseases or conditions, methods of assaying for or identifying a material that itself has no "specific and/or substantial utility", a method of making a material with no specific, substantial and credible utility and claims to intermediate products for use in making a final product with no specific, substantial and credible utility. In the instant case it appears that perfection of the required correlation would require further research to identify the appropriate genes, their correlation with a particular disease and their utility in either assays, screens or other methods which provide specific, substantial and credible utility. As previously set forth, because the claimed invention does not provide an identified gene which is up or down regulated, diagnostically correlated or useful to determine disease incidence, likelihood or cell differentiation state, applicants claims are directed to generally recognized research methods for which alone there is no specific and substantial utility or well established utility.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 31 and 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the term "the medium identified in Table I" the term lacks sufficient antecedent basis in the claim and further appears to attempt incorporation of certain elements as recited in a Table of the specification at p. 14. While the claims are read in light of the specification, the specification can not be read into the claims. Thus, where applicant's wish to limit the elements of the culture conditions such limitations are required to be recited in the claims. The artisan cannot discern the metes and bounds of the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

9. Claims 7, 32, 34 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., US Patent 5,672,499 filed June 7, 1995, issued September 30, 1997 and Claims 7, 32, 34 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., US Patent 6,001,654 filed April 25, 1997, issued Dec. 14, 1999.

As applicants continue to address the references jointly the rejection is also addressed jointly as the references are cumulative.

Applicants argue that the references fail to teach differentiation of immortalized neural crest cells into smooth muscle cells. Applicants further submit that primary culture cells are not immortalized as recognized in the art. Applicants acknowledge a prophetic example of immortalizing neural crest stem cells. Applicants submit that their population of smooth muscle cells are nearly 100% smooth muscle cells as noted at p. 15, line 4 but that neither patent teaches every (these) elements of the claims.

Applicants arguments filed 12-27-01 have been fully considered but are not persuasive. As acknowledged by applicants, the '654 and '499 references teach examples of immortalized neural crest stem cells which are immortalized in particular as disclosed at column 19, lines 27-55 of the '654 patent, including via transforming oncogenes of the preferred embodiment, oncogene v-myc. The procedures for such transformation and immortalization of neural crest stem cells is disclosed in particular at columns 31, line 45-column 32, line 25 of the '654 patent. Thus, the Anderson reference discloses immortalization of neural crest stem cells via v-myc transformation as claimed. Thus, the claimed invention is anticipated by the prior art disclosure.

As previously set forth it is noted that the method of Anderson results in the differentiation of smooth muscle cells and the identification of the gene alpha smooth muscle actin, peripherin and calponin which are up regulated upon differentiation in culture to smooth muscle cells, see for example Figure 20, 22, claims 6 and 21. The conditions suitable for smooth

muscle cell differentiation include those as disclosed in particular with TGF-β as noted in Figure 22 D-F and column 35, lines 47-63.

As to applicants new claim limitations, of expression of α-actin, calponin and SM22α, it is noted that Anderson is silent to expression of α-actin and SM22α. However as the transformed cells of Anderson are of a neural crest cell line immortalized via v-myc transformation, in the same manner as the preferred embodiment of the invention, and because Anderson's cells are differentiated into smooth muscle cells similarly to Applicant's, the cells would inherently and necessarily express α-actin, calponin and SM22α. The specification and art recognize that α-actin, calponin and SM22α genes are expressed in smooth muscle, see in particular p. 15, lines 23-28 of the specification. Similarly Anderson evidences that calponin and smooth muscle actin are expressed in smooth muscle cells. Both the cells of Applicants claims and Anderson are designated as smooth muscle cells. Therefore based on the specifications teachings that smooth muscle cells express α-actin, calponin and SM22α and the teachings of Anderson that the cells are smooth muscle cells and express calponin and smooth muscle actin, the cells are established as being the same. As the cells are the same i.e., they are smooth muscle actin cells, both the cells of Applicant's invention and Anderson would necessarily and inherently express the noted smooth muscle genes α-actin, calponin and SM22α, in addition to smooth muscle actin.

Thus absent evidence to the contrary, the teachings of Anderson that the cells of the '654 and '499 patents are smooth muscle cells would be sufficient for the artisan to conclude that the

cells would necessarily and inherently express the same genes established to be expressed in smooth muscle cells, namely α-actin, calponin and SM22α as claimed, even though the reference only acknowledges expression of smooth muscle actin and calponin.

Moreover, it is noted that in TGF-β cultures such as in Figure 22D-F, column, 5, lines 21-23 which teach 99% of the colonies (cells) in the TGFβ cultures as being smooth muscle cells, see also column 36, lines 47-63. Such cultures are provided with and without TGF-β1. In at least the TGFβ cultures, the smooth muscle cells are uniform as it is noted that 95-99%, i.e., nearly 100% of the cells are smooth muscle cells as claimed in claim 34. While the exemplary neural crest cells of Anderson are of rat origin, the specification makes clear that mammalian cells are embodied, see in particular column 5, lines 67-column 6, line 8, and thus Anderson is inclusive of murine neural crest cells as in claim 35. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., US Patent 5,672,499, Anderson et al., US Patent 6,001,654, Rao et al., J. of Neurobiology 32:722-746, 1997 and Sommer et al., Neuron 15:1245-58, 1995.

Anderson et al., Patents '654 and '499 are as set forth above and teach the methods of claims 7, 32, 34 and 35. Including the suitability of the method of identifying up and down regulation of gene expression in neural crest cells using neural crest cell lines transformed with v-myc.

Anderson et al., does not teach the method of claim 7, wherein the cells are Monc-1 cells.

Rao et al., teaches immortalized neural crest stem cells via transformation with v-myc which cells are termed Monc-1 cells, see in particular Abstract.

Sommer et al., also teach immortalized neural crest stem cells via transformation with v-myc which cells are termed Monc-1 cells, see in particular p. 1249, column 1, lines 7-17.

Thus, one of skill in the art would have been motivated to substitute the Monc-1 cells of Rao and Sommer in the method of Anderson, based on Anderson's teachings of the suitability of such v-myc transformed neural crest cells in the study of up and down regulation of gene expression during differentiation to smooth muscle cells. The appropriate conditions of culture

are disclosed in Anderson and Anderson exemplifies the success in the method as smooth muscle actin and calponin are disclosed as being up regulated while other neuronal or glial type genes are down regulated. Thus, the cumulative reference teachings render the claimed invention obvious to one of skill in the art.

Status of Claims

12. No claims are allowed.

Conclusion

13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
June 27, 2002

Gary L. Kunz
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